Improving Identification of Neuroactive Compounds using Temporal Information from Microelectrode Array Recordings of Cortical Neural Networks and a Semi-supervised Classification Algorithm

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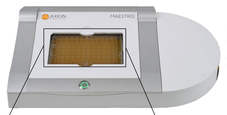
Introduction

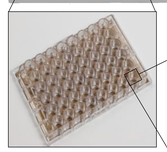
- **Exposure to environmental chemicals** can result in **acute neurotoxicity (NT)**, negatively impacting brain activity
- **In vitro microelectrode array (MEAs)** recordings of neural network function following chemical exposure are being used to screen chemicals for NT hazard (Acute Neurotoxicity (AcN))
- These recordings capture **temporal (from min to days)** and spatial **aspects of action potential activity**, which are described by a set of **network parameters (NPs)**
- To determine if a compound is neuroactive, **global NPs are extracted from 40 min neural recordings** resulting in **loss of temporal information (TI)**
- **In this work, our goal was to explore the properties of the TI to screen for acute neuroactive compounds using the response from a single high concentration (nominally 40 µM) and a window analysis technique**

Acute Neurotoxicity (AcN) Assay

Acute single-point screening is used to identify active compounds from large compound sets that are then screened in concentration-response format

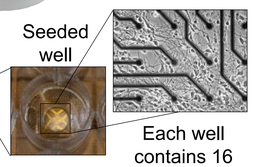


Maestro MEA system (Axion BioSystems)



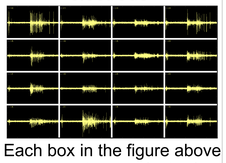
Multiwell culture plate

Seeded well



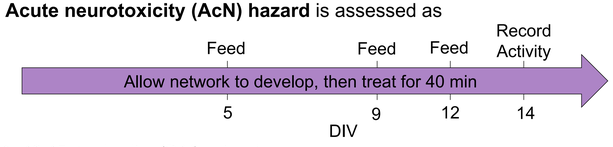
Each well contains 16 electrodes

Neural activity per electrode



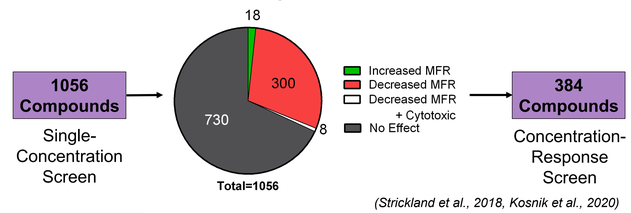
Each box in the figure above represents one electrode

Acute neurotoxicity (AcN) hazard is assessed as



- 13-15 day in vitro (DIV) networks
- Two 40 min (Baseline and Treated) recordings per plate.

Acute Effects of ToxCast compounds on Network Function



(Strickland et al., 2018, Kosnik et al., 2020)

U.S. Environmental Protection Agency
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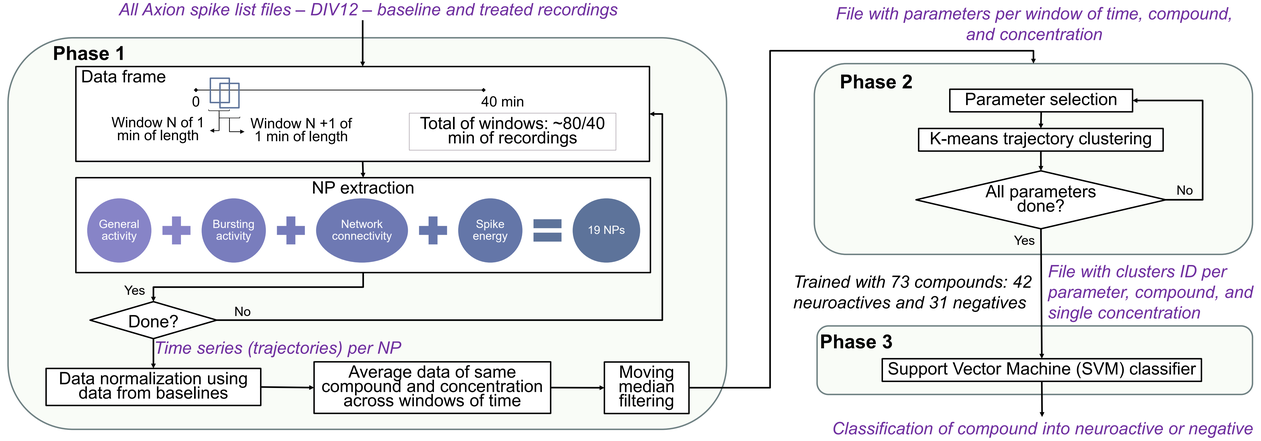
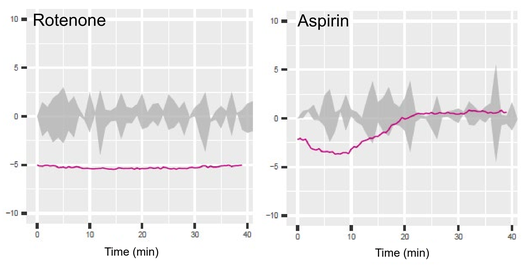
Method of Analysis

Objective: To use a window analysis technique, a variety of neural network parameters, and classification model fusion technique to explore how increasing the resolution of the temporal information of single-point recordings can help in the identification of neuroactive and negative compounds

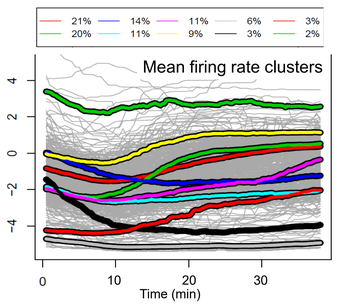


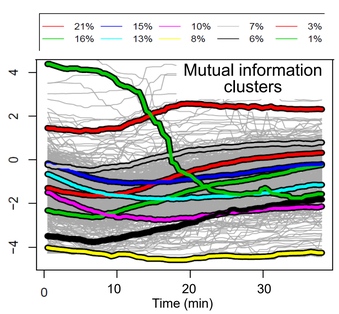
Results (1/2)

Trajectories for four compounds at 40µM for mean firing rate



K-means trajectory clusters for mean firing rate and mutual information





Confusion matrix of SVM classifier of proposed method

		Predicted	
		Neuroactive	*Negative*
True ID	*Neuroactive*	37	5
	Negative	0	31

Sensitivity: 88%, Specificity: 100%
Precision: 100%, Negative predictive value: 86%
Accuracy: 93%

- To evaluate the value of TI, the SVM classifier was trained with the same 73 compounds but excluding its TI:

Confusion matrix of SVM classifier without temporal information

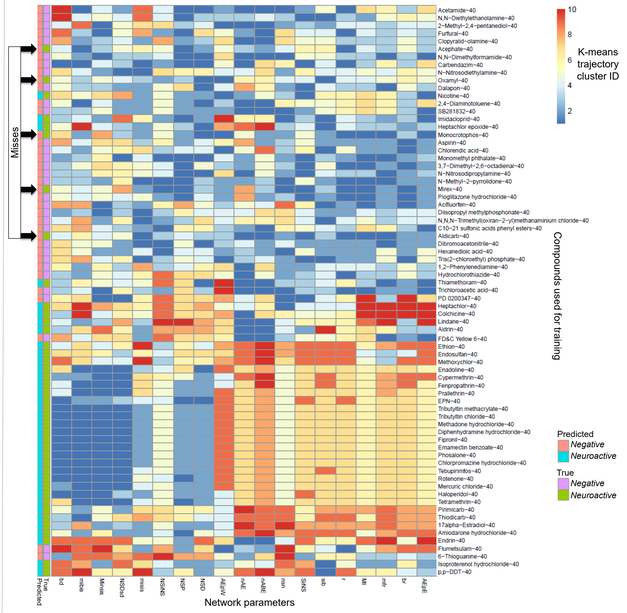
		Predicted	
		Neuroactive	*Negative*
True ID	*Neuroactive*	33	2
	Negative	8	30

Sensitivity: 94.3%, Specificity: 78.9%
Precision: 80.5%, Negative predictive value: 93%
Accuracy: 86.3%

Results (2/2)

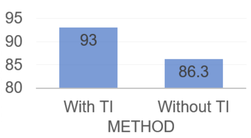
Heatmap of the classification results for the training dataset

- Shows clustering results from the k-means trajectory clustering and classification results from the SVM classifier



Summary and Conclusions

- SVM classifier accuracy results



- Using model to find neuroactive compounds:

384 compounds
127 negatives
257 neuroactives

- **The higher classification accuracy of the SVM model that uses TI data demonstrates including TI is more effective for identifying acute neuroactive compounds when performing single-point screening**

References

- Strickland JD, Martin M, Houck T, Richard A and Shafer TJ. Screening the ToxCast Phase II Libraries for Neuroactivity using Cortical Neurons Grown on Multi-well Microelectrode Array (mwMEA) Plates. Archives of Toxicology. 2018. 92, 487-500.
- Kosnik M, Strickland JD, Marvel S, Wallace K, Richard AM, Reif DM and Shafer TJ. Concentration-Response Evaluation of ToxCast Compounds for Multivariate Fingerprints of Neural Network Function. Archives of Toxicology, Accepted November 26, 2019.

This poster does not represent Agency Policy.

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